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Randomized, Placebo-Controlled, Double-Blind Study of Ropinirole in Chronic Stroke

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Background and Purpose—Evidence suggests the potential to improve motor status in patients with stroke by modifying brain catecholaminergic tone. The current study hypothesized that increased dopaminergic tone via the dopamine agonist ropinirole, when combined with physiotherapy (PT), would significantly and safely increase gait velocity.

Methods—Patients with moderate motor deficits due to stroke 1 to 12 months prior were randomized (double blinded) to 9 weeks of immediate-release ropinirole or placebo, each with PT, and followed up for 3 additional weeks. Drug dose (0.25 to 4 mg once daily) was titrated weekly, as tolerated. The primary end point was gait velocity during the 12 weeks of study participation.

Results—Patients in the ropinirole+PT group averaged 2.4 mg/d by end of week 9, although the target dose was at least 3 mg/d. Ropinirole+PT was generally safe and well tolerated, including no drug-related serious adverse events. Across all 33 enrollees, significant gains were found over time for gait velocity and for most secondary end points. However, gains did not differ by treatment assignment. PT and occupational therapy were commonly prescribed outside of the trial, although the extent of these was not correlated with study outcomes.

Conclusions—At doses achieved in this trial, increased dopaminergic tone via ropinirole+PT was generally well tolerated but did not show any improvement over and above the effects of PT alone. (*Stroke*. 2009;40:3034-3038.)

Key Words: stroke treatment ■ stroke recovery

Stroke is a major source of disability. One approach to reducing poststroke disability is to maximize the function of surviving brain elements, with suggested therapeutic targets in both the acute and chronic phases.^{1,2} One such restorative approach is to modify tone within specific neurochemical systems, particularly catecholaminergic systems. Some,^{3,4} though not all,^{5,6} studies of drugs that broadly increase activity within central nervous system (CNS) catecholaminergic systems have suggested a favorable effect on motor status after stroke. The precise CNS catecholamine system affected by these studies is unclear because the compounds evaluated have generally acted on multiple catecholaminergic receptors.

The purpose of the current study was to extend these prior observations of pharmacologic promotion of motor system restoration after stroke by evaluating a drug that acts on a single catecholaminergic system, dopamine. Modulating brain dopaminergic tone was not intended to replace a proposed poststroke dopamine deficit, as with Parkinson disease, although focal changes in brain dopaminergic tone have been described after stroke.⁷⁻⁹ Instead,

the intent was to favorably affect processes that are known to be dopamine responsive and that are also relevant to behavioral recovery after stroke, such as mood, memory, reward, motivation, attention, learning, movement, and plasticity.¹⁰⁻¹⁴ Each of these processes might be a means by which increased dopaminergic tone after stroke might improve CNS function.

The current study was a randomized, double-blind, placebo-controlled trial to evaluate the effects of the DA2 dopaminergic agonist, immediate-release ropinirole, on gait and related motor functions in patients in the early phase of chronic stroke. The primary study hypothesis was that ropinirole, when combined with physiotherapy (PT) during peak serum drug levels, would result in greater gains compared with placebo+PT during the 12 weeks of study participation. The primary end point was gait velocity, which is commonly affected after stroke¹⁵ and is linked to outcomes and participation.¹⁶ Secondary end points were safety, gait endurance, general leg motor function measured as the leg Fugl-Meyer (FM) score, plus the aforementioned measures when examined during a shorter time interval (9 weeks).

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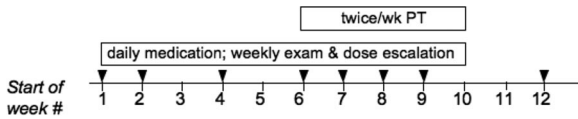


Figure 1. Time course of the study. After completing baseline studies, subjects received 9 weeks of daily study medication, either ropinirole or placebo, with weekly safety visits during these 9 weeks. Beginning at week 6, 4 weeks of twice-weekly PT began. After a 3-week washout period, the final examination was administered. Triangles indicate times when gait velocity, the primary end point, was measured.

Subjects and Methods

Subjects and Study Overview

The main entry criteria were ischemic or hemorrhagic stroke 1 to 12 months prior to the study, age 18 to 80 years, prestroke modified Rankin score <2 , and motor deficits (arm/leg FM motor score 23 to 83 out of 100). Exclusion criteria included major depression; gait difficulty that was either very mild (50-foot walk <15 seconds) or severe (FM ambulation score <3) in magnitude; a substantial decrease in alertness, language reception, or attention; pregnant or lactating; advanced systemic medical disease; coexistent major neurologic or psychiatric disease; orthostatic hypotension; concurrent use of drugs known to interfere with the action of ropinirole; concurrent enrollment in another stroke recovery investigation; or any contraindication to ropinirole. The choice of at least 1 month after stroke was intended to ensure that acute stroke medical issues would have reached resolution and also that enrollees would have completed standard inpatient poststroke rehabilitation. The choice of no more than 12 months after stroke was intended to minimize the variance introduced by late poststroke changes, eg, contractures and psychosocial decline.

After informed consent was obtained, eligibility was determined and eligible subjects were randomized in a 1:1 fashion to either immediate-release ropinirole or placebo in a double-blind manner. Separate randomizations were used for subjects <3 months after stroke ("early group"), and subjects ≥ 3 months after stroke ("late group"); the 3-month cutoff was selected because many motor behaviors reach a plateau at ≈ 3 months after stroke.¹⁷ Computer-generated randomization schedules were generated for each site, with envelopes connecting subject identification to treatment arm assignment provided to each site's unblinded pharmacist. Patients received either drug or placebo for 9 weeks, with concomitant PT for the last 4 of these weeks (Figure 1). Assessments were performed weekly for 9 weeks. Final assessments were done at week 12, ie, 3 weeks after the end of drug therapy. Local institutional review boards approved all procedures.

Therapeutic Intervention

In sum, drug dose was once daily and was titrated upward as tolerated during the 9-week treatment period. For 4 weeks (the start of week 6 to the end of week 9), a 90-minute standardized regimen of PT was introduced, twice weekly, at peak drug levels, ie, ≈ 1 hour after ingestion.

Ropinirole is a medication that requires titrating. Thus, there were 9 visits at which drug tolerability/safety was assessed, the dose was advanced as appropriate, and a new blister pack of pills was dispensed. Each of these visits began with safety assessments that consisted of review of concomitant medications, new symptoms, and a check for orthostatic hypotension (drop of systolic or diastolic blood pressure >15 mm Hg). For weeks 2 to 9, compliance was also ascertained, with noncompliance defined as missing ≥ 3 of the 7 doses. After these assessments, the next week's pill pack was ordered.

For week 1, the pill was either placebo or ropinirole at the 0.25-mg dose. Dosing was oral and daily throughout the study. For weeks 2 to 9, the dose was either the next highest dose according to the schedule for dose advancement, if appropriate, or a lower dose, based on the presence of any suspected drug-related side effects. The

subject was observed for 2 hours after ingesting the first pill at each dose. The schedule for dose advancement was, for week 1, 0.25 mg; week 2, 0.5 mg; week 3, 0.75 mg; week 4, 1 mg; week 5, 1.5 mg; week 6, 2 mg; week 7, 2.5 mg; week 8, 3 mg; and week 9, 4 mg. Note that the target was to have each patient reach at least 3 mg/d to approximate the biologic effect achieved in a prior study of 100 mg/d L-dopa.⁴ Although that prior study evaluated L-dopa, which must be metabolized to become dopamine, and the current study evaluated ropinirole, which is a DA₂ dopaminergic agonist, the 2 have similar biologic effects on brain dopaminergic tone. In all instances, the size, color, weight, and number of pills to meet the ropinirole dose were matched by the placebo pills.

For 4 weeks, from the start of week 6 to the end of week 9, PT was introduced, twice weekly, for 90 minutes per session, standardized across sites. Each PT session began 60 minutes after pill ingestion and had 60 minutes focused on gait therapy and 30 minutes on arm therapy. Subjects were discharged home with written instructions for performance of home PT exercises, which prescribed at least 30 minutes/d of individually selected arm and leg exercises to be started 30 to 60 minutes after study pill ingestion.

Behavioral Testing

Baseline assessments included the Hamilton Depression Scale (17-item version), Barthel Index, Stroke Impact Scale-16 (SIS-16), arm and leg FM motor scales, gait velocity, and gait endurance. Gait velocity was measured over a 50-foot (15.24 meters) hallway, with the better of 2 efforts recorded. Gait endurance measured either the distance walked up/down this hallway for 6 minutes or the distance walked over time until the subject needed to stop (if <6 minutes). Whenever possible, the same therapist performed all assessments for a given patient over time.

Gait velocity, gait endurance, and FM scores were reassessed 7 more times to week 12; SIS-16, 4 more times; and the Barthel Index and the Hamilton Depression Scale, 2 more times. Gait studies and FM scoring were performed 30 to 60 minutes after study drug ingestion. At the end of week 12, each subject was asked to guess which treatment group he/she was randomized to, and the results were recorded. At all visits, adverse events, amount of therapy received outside the study, and concomitant medications were reviewed.

Statistics

Statistical analyses included 2-tailed parametric methods. Continuous variables were compared by ANOVA testing; categorical variables, by Fisher's exact test. Missing data were imputed by carrying the last measured value forward.

Initial power estimates, adapted from Sullivan et al,¹⁸ anticipated a baseline gait velocity of 0.35 ± 0.6 m/s (mean \pm SD) and end-of-treatment gait velocities of 0.49 m/s for subjects in the ropinirole+PT group versus 0.41 m/s for those in the placebo+PT group. This suggested that 26 patients were required in each study arm to achieve 80% power at $\alpha=0.05$. Preliminary analysis of blinded data from 24 patients disclosed mean baseline gait velocities of 0.55 ± 0.31 m/s at baseline and 0.71 ± 0.39 m/s across the 2 groups at the end of study drug administration, leading to a revised sample size estimate of 17 patients in each study arm.

Results

Subjects

A total of 744 patients were screened from February 2004 to February 2007, of whom 33 patients were enrolled: 25 from the University of California Irvine, 4 from UCLA, and 4 from the University of Texas at Houston. The most common reasons for screening failure were that the patient was too strong (211), spoke no English (86), was too weak (82), was >1 year after stroke (65), declined participation (45), or had psychiatric comorbidity, including dementia (35).

Of the 33 enrolled, 7 were <3 months after stroke ("early"; 3 randomized to placebo+PT and 4 to ropinirole+PT), and

Table 1. Baseline Assessments

	Ropinirole+PT (n=17)	Placebo+PT (n=16)	P
Age, y	63±13	60±15	0.47
Sex, M/F	11/6	12/4	0.71
Time after stroke, d	192±97	233±110	0.26
Index stroke was first stroke	14	12	1.0
Smoking history, >10 pack-y	3	2	1.0
Previously diagnosed with			
Hypertension	11	10	1.0
Hyperlipidemia	12	12	0.69
Diabetes mellitus	5	0	0.046
Atrial fibrillation	0	0	1.0
Coronary artery disease	3	1	0.60
Baseline value for			
Gait velocity, m/s	0.54±0.37	0.49±0.28	0.67
Leg FM score	21±5	23±6	0.38
Arm FM score	32±17	26±17	0.34
Gait endurance (m over 6 min)	140±103	134±82	0.86
Hamilton depression score	7±4	4±3	0.048
FIM ambulation score	5.2±1.3	5.4±1.1	0.57
Barthel Index	81±20	80±16	0.85
SIS-16	56±10	58±11	0.65

Normal FM scores are 66 for the arm, 34 for the leg. Values are mean±SD or numbers of subjects, as appropriate.

26 were ≥3 months after stroke (“late”; 13 subjects in each group). Overall, at baseline, subjects were well matched across the 2 treatment groups, although a significant excess of diabetes was present in the ropinirole+PT group (Table 1). The distribution of stroke subtypes did not differ between treatment groups ($P>0.9$). Rankin Scale scores at baseline did not differ between groups, being 0 to 1 in all but 1 subject.

Study Therapy and Safety

Medication dose was advanced according to the schedule more often in the placebo+PT group than in the ropinirole+PT group. Thus, in the placebo+PT group, the peak dose averaged 3.6 ± 0.9 mg, and 13 patients reached the 4-mg/d dose at week 9; note that this was a virtual dose, because no active drug was actually given to subjects in the placebo+PT group. However, in the ropinirole+PT group, the peak daily dose averaged 2.4 ± 1.2 mg, and only 4 patients reaching the 4-mg/d dose at week 9. Medication compliance was high, because only 3 patients (2 in the ropinirole+PT group and 1 in the placebo+PT group) had a week of noncompliance.

Overall, ropinirole+PT was generally safe and well tolerated. Five serious adverse events occurred, none of which was attributed to ropinirole+PT. One of these, falling, was deemed possibly or probably related to study medication by blinded study personnel; this patient was later learned to be in the placebo+PT group. The other 4 serious adverse events (new ischemic stroke, urinary tract infection, facial sensorimotor symptoms, and death from bile duct cancer) were each thought by blinded study personnel to be unrelated to the study medication. These 4 patients were all in the ropinirole+PT group. Nonserious adverse events present in at least 5 patients and deemed possibly or probably related to the study medication by blinded study personnel included sleepiness (8/1), fatigue (6/0), and dizziness (3/2) (No. in the ropinirole+PT group/No. in the placebo+PT group).

Outside Therapy

Therapy prescribed by the enrollee’s caregivers during study enrollment, and thus outside of study activities, was allowed by the protocol and was common (Table 2). PT was administered most often; occupational therapy, most intensively (ie, highest number of sessions). Subjects in the placebo+PT group were significantly more likely to receive PT.

Behavioral Effects

Across all subjects, significant gains in gait velocity were seen from baseline to week 12, being 0.22 ± 0.21 m/s, ie, 42%, higher than at baseline (repeated-measures ANOVA, $P<0.0001$). Gains were also significant to week 9 ($P=0.0001$). Significant gains were also seen at both time points for gait endurance, leg FM score, and SIS-16 score. Changes in arm FM score and Barthel Index were not significant at either time point. Interestingly, from baseline to week 4, before any PT, significant gains were seen for gait velocity, gait endurance, and SIS-16 score. Note that these gains from baseline to week 4 were smaller in patients with more chronic stroke, such that the extent of gains was inversely related to the number of days after stroke at the time of study enrollment for gait velocity ($P<0.05$) and for gait endurance ($P<0.06$).

No differences between treatment groups were apparent at the end of either treatment or study, however, because the time×group interaction term (repeated-measures ANOVA) was not significant at either time point for gait velocity (Figure 2), gait endurance, leg FM score, SIS-16 score, arm FM score, or Barthel Index. The lack of difference between treatment groups remained true when only subjects in the “early” group were evaluated and when only subjects in the “late” group were evaluated. In addition, no significance was present when gait velocity, gait endurance, and leg FM score

Table 2. Therapy Received by Patients Outside of the Study

Type of Therapy	No. of Subjects Receiving Any Outside Therapy During Study Participation in the Ropinirole+PT Group (n=17)	No. of Subjects Receiving Any Outside Therapy During Study Participation in the Placebo+PT Group (n=16)	P	Mean No. of Sessions
Occupational therapy	4	4	1.0	21
Physical therapy	7	13	0.03	12
Speech therapy	4	1	0.34	19

Mean No. of sessions is the mean among both groups for those patients who did receive outside therapy.

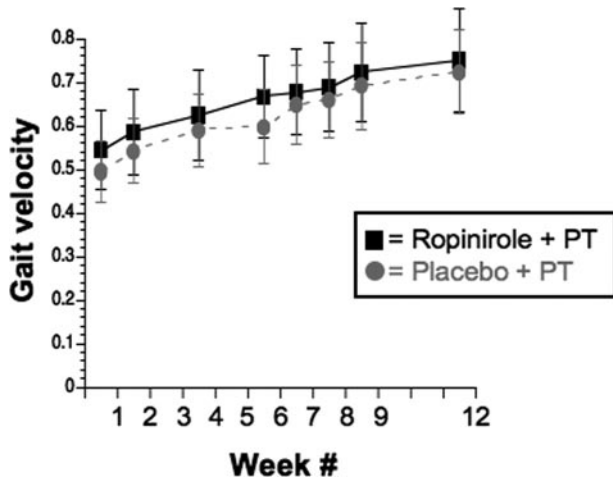


Figure 2. Main study result. Across all subjects, gait velocity improved significantly over time, from baseline to week 4, to week 9, and to week 12. However, there were no significant differences according to treatment group for any of these time intervals.

were further examined by adding terms for either time after stroke or the total number of all outside therapy sessions. Furthermore, neither total number of all outside therapy sessions nor total number of PT sessions was correlated with a change in any primary or secondary end point to week 9 or 12. Note that repeated-measures ANOVA found significant ($P < 0.03$) gains in gait velocity during the 12 weeks when we examined the subjects in the ropinirole+PT group only and when we examining the subjects in the placebo+PT group only.

Medication Effects and Blinding

Medication effects overcame blinding in the ropinirole+PT group in nearly all cases. Among the 14 patients randomized to ropinirole+PT who ventured a guess at week 12 as to treatment assignment, 13 of 14 (93%) guessed correctly. In the placebo+PT group, guesses were at chance level, as 8 of 15 (53%) guessed correctly, a proportion of correct guesses that is significantly ($P < 0.02$) lower compared with that in the ropinirole+PT group.

Discussion

Several lines of evidence suggest that increased CNS dopaminergic tone might be useful for restoring function after stroke, given the key role this neurotransmitter has on mood, memory, reward, motivation, attention, learning, movement, and plasticity.^{10–14} This study aimed to evaluate safety and gait/motor effects of ropinirole+PT in patients with chronic stroke. Ropinirole+PT was safe and well tolerated. Across all subjects, significant gains were found for gait velocity and other motor measures, but there was no difference between the 2 treatment arms.

The main study hypothesis was that ropinirole+PT was superior to placebo+PT for increasing gait velocity, but the data did not support this. There are several possible interpretations. First, the findings might in part reflect baseline imbalances, with higher diabetes prevalence and depression (Table 1) and less outside PT (Table 2) possibly reducing the

extent of gait improvement in the ropinirole+PT group. Second, the findings might indicate that increased dopaminergic tone simply does not improve motor function after stroke, a view supported by some^{19,20} but not other^{21,22} preclinical studies. Furthermore in this regard, some of the heterogeneity in ropinirole effects might stem from the fact that dopaminergic influences vary according to basal dopamine level,²³ and these levels might vary in relation to features of stroke injury, a possible consideration for future trials. Third, the intensity and duration of PT were modest, which might have limited the ability to detect a difference in treatment groups.²⁴ Fourth, subjects in the ropinirole+PT group were able to guess treatment assignment in all but 1 case, whereas subjects in the placebo+PT group guessed at chance, possibly indicating the presence of an expectation bias. Fifth, variability in time after stroke at study entry might indicate the coexistence of several biologically distinct patient subgroups.

An additional interpretation of the current results is that the study hypothesis was not fully investigated. Patients in the ropinirole+PT group reached an average daily dose of 2.4 ± 1.2 mg by week 9, indeed spending most of the 9 weeks at a dose lower than this, all lower than the 3-mg/d target. Whether higher doses of ropinirole would be superior to placebo in improving motor function after stroke remains to be determined. For the aforementioned reasons and because this study enrolled a small number of patients with mixed stroke subtypes, the current report must not be considered conclusive, instead indicating a need for further investigation of the effects of modulating dopaminergic tone after stroke.

Some observations might be of value to future trials of restorative therapies targeting patients with stroke. Gait velocity and other measures were significantly improved by study week 4, ie, before initiation of PT in either group and at a time when the dose of ropinirole was still very low. This finding might reflect incomplete spontaneous recovery in some patients at the time of study entry (supported by the inverse relation between time after stroke and gains to week 4), overcoming of learned disuse, effects of repeated testing, or direct psychosocial effects of study participation.²⁵ Second, outside therapy was common among subjects in both treatment arms. Although the amount of such therapy had little relation to outcomes in the current study, experience is nonetheless important in shaping outcome after stroke and in enabling restorative therapies,²⁶ and might therefore be important in other studies. Furthermore, poststroke rehabilitation is highly variable in some countries and difficult to control in others, providing an additional reason to measure its extent in a clinical trial context.

Across all patients in this study, significant improvements in gait velocity and other motor assessments were found over time. At doses achieved in this trial, ropinirole+PT was generally safe and well tolerated; however, this combination did not show any improvement over and above the effects of placebo+PT. PT was commonly prescribed outside of study activities and so represents a potential confounder in restorative trials.

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Disclosures

Dr Cramer is on the Advisory Board of, and has received consulting fees from, GlaxoSmithKline. Lori A. Enney is an employee of GlaxoSmithKline.

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